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REVIEW ARTICLE

VIA MEDICA

Risk assessment of recurrent venous thromboembolism

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Abstract

Venous thromboembolism (VTE) recurrence risk is determined by risk factors that were present at the time of the initial VTE episode. The most significant determinant of risk for recurrent VTE is whether the VTE occurred in the setting of provoked or unprovoked condition. As anticoagulation reduces the risk of recurrent VTE, initial anticoagulant treatment at the time of VTE diagnosis is indicated with consideration given to an associated risk of bleeding. After three months of initial anticoagulation, recurrence risk and bleeding risk should be assessed again to decide if anticoagulation should be stopped or continued indefinitely. If indefinite anticoagulation is recommended, annual assessment of both risks should guide decisions about further treatment. Knowledge about the various risk factors for VTE recurrence and the risk factors for bleeding associated with anticoagulation should guide anticoagulant duration.

Key words: venous thromboembolism recurrence, venous thromboembolism risk factors, anticoagulant treatment, anti-vitamin K drugs, direct oral anticoagulant drugs, bleeding risk assessment

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Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), affects 1–2 in 1,000 individuals annually and is the third most common cause of vascular death worldwide [1]. VTE is also a cause of considerable long-term disability connected with post-thrombotic syndrome, chronic exertional dyspnea, and chronic thromboembolic pulmonary hypertension. Anticoagulant therapy is the mainstay of VTE treatment, and can substantially reduce morbidity, mortality and health costs [2]. However, such therapy, especially using vitamin K antagonists (VKA), confers an increased risk of potentially devastating bleeding complications. For this reason, recent guidelines recommend after a VTE episode an obligatory 3-month primary anticoagulant treatment, after which a decision should be made to either stop anticoagulation or continue it as a long-term secondary prevention [3]. This decision is based on the balance between the risk of recurrence if treatment is stopped, and the risk of bleeding when treatment is continued [3]. Recent guidelines recommend indefinite duration of anticoagulation in patients with high recurrence risk and a low risk of bleeding, with consideration given to patient preference [3, 4]. Risks of VTE recurrence and bleeding should be reassessed at least annually [4].

Risk factors for VTE recurrence

Traditionally, according to the circumstances in which a VTE event occurred, the risk of VTE recurrence was dichotomized. Patients with a high risk of recurrence, namely those with unprovoked VTE (c.10% at 1 year, 30% at 5 years), and those with VTE provoked by a major persistent risk factor, such as cancer (15% during first year), required extended (indefinite) anticoagulant therapy. On the other hand, patients with low recurrence rate with VTE provoked by a major transient risk factor (e.g. major surgery or

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Table I. One- and 5-year recurrence rates following discontinuation of anticoagulant therapy according to risk factor category [5]

Risk factor category	VTE recurrence rate	
	1-year [%]	5-year [%]
Major transient	1	3
Major persistent	15	NC
Minor transient	4–6	15
Minor persistent	11	~30
Unprovoked	8–10	30

NC — not calculable (due to high cancer mortality)

trauma) required anticoagulant therapy for three months only [4]. More recently, this simplistic distinction has been challenged. Minor risk factors, persistent and transient, have been identified with risk of recurrence often similar to that of unprovoked VTE (see Table I) [5]. According to the International Society on Thrombosis and Hemostasis (ISTH), risk factors were defined as minor if they were associated with half the risk of recurrent VTE after stopping anticoagulants compared to patients with no risk factors, or were associated with a 3–10-fold increased risk of having a first VTE [6]. Those minor risk factors broadened the group of VTE patients with the recommendation for long-term secondary VTE prevention [7].

A systematic review published just over 10 years ago showed yet another example of these differences between various transient risk factors, demonstrating that while after 24 months patients with a surgical risk factor have a VTE recurrence rate of 0.7%, those with a nonsurgical transient risk factor showed a recurrence rate of 4.3% [8].

Recently, based on the index VTE event, two major guidelines have provided a framework for categorizing VTE risk factors. Although they differ a little in terminology, their categorization is broadly similar (Table II) [3, 9].

Anticoagulant treatment was dominated for decades by heparin and VKA. The advent of direct oral anticoagulants (DOACs) changed this picture dramatically. With their fixed-dose oral administration, and markedly reduced rate of devastating central nervous system bleeding, DOACs are now replacing VKA in initial and extended anticoagulant VTE treatment [3, 9]. Several trials have been performed to assess their use showing that dabigatran [10], apixaban [11], and rivaroxaban [12] are both safe and effective in this setting. To further individualize patients' VTE recurrence risk, several other persistent and transient minor risk factors have been included in these trials. Their conferred risk of recurrence has been described by a hazard ratio (HR) and its 95% confidence interval (CI) compared to patients not carrying this risk. Those additional risk factors not mentioned in Table II are listed in Table III.

Table II. Categorization of venous thromboembolism (VTE) risk factors (modified after [3, 9])

VTE PROVOKED BY TRANSIENT RISK FACTOR (Resolves after it has provoked VTE)
Major transient risk factors (during three months before VTE episode; recurrence risk <3%/year)
Recent major surgery (with general anesthesia for ≥30 min.) or major trauma with fractures
Confinement to bed in hospital (at least three days; with an acute illness)
Cesarean section
Minor transient risk factors (during two months before VTE episode; recurrence risk 3–8%/year)
Surgery (with general anesthesia for <30 min.)
Admission to hospital for <3 days with an acute illness
Estrogen therapy (e.g. oral contraceptives, hormone replacement therapy)
Pregnancy and puerperium
Confined to bed out of hospital for ≥3 days
Leg injury associated with reduced mobility for ≥3 days
Long haul flight
VTE PROVOKED BY PERSISTENT RISK FACTOR (Persists after it has provoked VTE)
Major persistent risk factors (recurrence risk >8%/year)
Active cancer (e.g. ongoing chemotherapy, recurrent or progressive disease)
Antiphospholipid syndrome (triple positive)
Minor persistent risk factors
Inflammatory bowel disease
Autoimmune disorders (systemic)
Chronic immobility (e.g. spinal cord injury)
UNPROVOKED VTE (No identified provoking risk factor)

Hormone-provoked VTE includes a VTE episode related to pregnancy and puerperium, and hormone use (mainly of estrogen-containing oral contraceptives and hormone replacement therapy). Optimal duration of pregnancy-related VTE treatment has yet to be established, but it is recommended to use low molecular heparin during pregnancy and at least six weeks postpartum and then use VKA for a total of three months, as DOACs are contraindicated during lactation [7, 13].

Oral hormone therapy is considered a minor transient risk factor with low risk of VTE recurrence providing that estrogen therapy is stopped. Of note, the risk is highest in the 6–12 months after initiating therapy. Additional risk factors may modulate the recurrence risk in women with hormone-provoked VTE (see infra; HERDOO2 rule).

Table III. Risk for venous thromboembolism (VTE) recurrence: minor persistent and transient risk factors (modified after [7])

Persistent factor	Reported risk HR (95% CI)	Remarks
Renal impairment	5.32 (1.49–18.95)	eGFR <60 mL/min/1.73 m^2
Thrombophilia	1.4–1.9 (1.0–2.2)	Depending on inherited defect
Chronic heart failure	1.43 (1.04–1.97)	
Family history of VTE	1.2–1.92 (1.10–2.58)	Depending on whether both parents, a sibling, or just one parent suffered an episode
Obesity	1.6 (1.0–2.4)	BMI ≥30 kg/m^2
Transient factor		
Oral estrogen therapy	6.4 (1.5–27.3)	Estrogen based replacement therapy
Immobilization	2.9 (1.2–7.5)	Due to chronic medical disease

HR — hazard ratio; CI — confidence interval; eGFR — estimated glomerular filtration rate; BMI — body mass index

Among non-environmental risk factors, the influence of inherited thrombophilia on recurrent VTE is less clear. Most studies show a VTE recurrence rate not different from those without such genetic polymorphism/mutation (for review see [12]). Male sex carries a doubled risk of VTE recurrence compared to women, but only in those with unprovoked VTE [14]. The available evidence suggests that many patients with minor persistent risk factors may benefit from extended anticoagulant therapy, as do patients with major risk factors and those with truly unprovoked VTE.

A few other factors have been implicated as markers of personal risk of VTE recurrence with a potential to guide the decision as to the optimal duration of anticoagulation. They include: D-dimer levels (during anticoagulant treatment, or one month after stopping anticoagulation), and residual vein thrombosis (assessed by ultrasonography) or occlusion [13].

Predicting risk of recurrent thromboembolism and bleeding

Attempts have been made in the past to create more or less complex tools to predict personal risk of VTE recurrence in subjects after their first VTE episode. Risk prediction models may also help physicians to inform patients about risks and benefits of proposed treatment and then take into account patient preferences.

Several risk prediction models have been developed, including: the HERDOO2 rule [15, 16], the Vienna prediction model [17], and the DASH score [18]. Most of these risk models include only patients with unprovoked VTE. They use various combinations of factors: sex, age, body mass index (BMI), D-dimer levels, location and type of VTE event, and hormonal therapy to predict the risk. Only one of these models has been prospectively validated. This study (REVERSE II) used the HERDOO2 rule [hyperpigmentation, edema, and redness (HER) in either leg; D-dimer ≥250 µg/L; BMI ≥30 kg/m^2; age ≥65 years]) to determine if low risk patients with unprovoked VTE could safely stop anticoagulant therapy after 5–7 months of treatment [16]. It was shown that low-risk women (score ≤1) who stopped treatment had a recurrence rate of 3% (CI 1.8–4.8%)/patient-year, while high-risk women and men who discontinued treatment showed a recurrence rate of 8.1% (CI 5.2–11.9%). However, if they both continued treatment, the recurrence rate was only 1.6% (CI 1.1–2.3%) [16]. Recently, the REVERSE study investigators showed that in low-risk women (according to the HERDOO2 rule) with combined oral contraceptive (COC)-associated VTE, the risk of recurrent VTE was clearly lower (0.4% a year, 95% CI: 0.0–2.1%), compared to high-risk women (3.5% a year; 95% CI: 0.4–12.5%) [19].

Anticoagulation with VKA is associated with a 1–2% annual risk of major bleeding but it may vary substantially depending on additional risk factors. The two most used prognostic models for bleeding in VTE are the ACCP model [4] and VTE-BLEED [20, 21]. The first includes the following bleeding predictors: age >65 years, previous bleeding, cancer, metastatic cancer, renal failure, liver failure, thrombocytopenia, previous stroke, diabetes, anemia, antiplatelet therapy, non-steroidal anti-inflammatory drugs, poor anticoagulant control, comorbidity and reduced functional capacity, recent surgery, frequent falls, and alcohol abuse. One point is ascribed to each factor. Low risk of bleeding =0 points (0.8%); intermediate risk =1 point (1.6%); high risk ≥2 points (≥6.5%) [4].

VTE-BLEED bleeding risk factors, assigned points and associated risk of bleeding are shown in Table IV.

However, due to methodological limitations and insufficient predictive accuracy, recent guidelines [3] and a systematic review of available data [22] do not support, and in fact suggest against, routine use of prediction models in patients with venous thromboembolism. However, American Society of Hematology (ASH) guidelines [3] consider the use of scores for recurrence and bleeding in certain individual situations where their use may aid final

Table IV. VTE-BLEED bleeding prognostic model in venous thromboembolism

Predictor	Assigned points
Active cancer	2
Male sex	1
Uncontrolled hypertension (men)	1
Anemia	1.5
History of bleeding	1.5
Renal dysfunction (eGFR 30–60 mL/min/1,73 m^2)	1.5
Age ≥60 years	1

Bleeding risk 0–1 point: 2.8%; ≥2 points: 12.6%
eGFR — estimated glomerular filtration rate

decision-making regarding whether to continue or stop anticoagulation.

Long-term secondary VTE prevention in era of DOAC

The decision to extend anticoagulant treatment beyond three months as a secondary prevention of VTE recurrence depends on the associated benefits versus risks. These risks may change over time. For this reason, patients receiving extended anticoagulation should be reassessed at least annually [4]. Recent guidelines define low risk of recurrence at <3% a year if anticoagulation is stopped after 3-month primary treatment [3, 9]. It has to be remembered that while anticoagulation reduces the risk of recurrent VTE, this benefit does not persist after discontinuation of anticoagulation [23].

The introduction of DOAC completely changed the picture of VTE treatment. They are easy-to-use fixed-dose oral drugs with no requirement for laboratory monitoring. Moreover, DOACs are associated with a significantly (40%) lower risk of major bleeding and an impressively (60%+) lower risk of intracranial bleeding compared to VKA [24].

Successful DOAC trials in the primary treatment of VTE were followed by trials with DOAC use in secondary VTE prevention. Drugs were administered usually for 12 months after completing primary treatment (6–12 months). Dabigatran in a dose of 150 mg bid was used in the RE-MEDY trial and compared to warfarin [10]. Dabigatran was shown to be noninferior to warfarin in reducing the rate of recurrent or fatal VTE with a significantly lower (c.45%) rate of major or clinically relevant non-major bleeding (CRNM) compared to warfarin (5.6% vs. 10.2%, HR 0.54, 95% CI: 0.41–0.71, p <0.001). Interestingly, the EINSTEIN CHOICE and AMPLIFY-EXT trials used not only full anticoagulant doses but also reduced doses of rivaroxaban (20 mg and 10 mg od) and apixaban (5 mg and 2.5 mg bid), respectively [11, 12]. It was shown that both doses were effective and comparable in reducing the risk of recurrent VTE and all-cause mortality (by about 65%, to 3.8–4.2%; apixaban) as compared to placebo and of recurrent VTE as compared to aspirin (by about 70%, to 1.2–1.5% a year; rivaroxaban). While apixaban did not significantly increase the rate of major and CRNM bleeding as compared to placebo, rivaroxaban in both doses showed similar rates of major bleeding as aspirin (c.0.3–0.5%).

Pooled analysis of rivaroxaban used for secondary VTE prevention in patients with minor persistent risk factors showed that, even if numerically different, overall rate of recurrence in patients with minor persistent risk factors was statistically similar to that observed with unprovoked VTE (HR 0.68, 95% CI: 0.32–1.30%) [6]. This opens up an intriguing possibility of safely prolonging anticoagulation with a low-dose DOAC regimen in a large group of patients with various minor persistent or transient VTE risk factors deemed at higher risk of VTE recurrence. At this point, it is suggested that before switching to a low-dose regimen, patients should complete six months of full-dose primary treatment with rivaroxaban or apixaban, as for now all secondary prevention clinical trials start after six months of primary anticoagulation [6]. Probably, patients who should remain on high-dose regimens include those at high risk of recurrence (cancer, triple positive antiphospholipid syndrome), or those who had a recurrence on a reduced-dose regimen.

Patient preference would also be important as in those with a life-threatening pulmonary embolism or family history of fatal PE. On the other hand, a low-dose regimen could be preferred by patients participating in contact sports or those with a history of bleeding [25].

The benefit-risk profile of extending anticoagulation in the era of low-dose DOACs is clearly different to what it was in the VKA era. More trials are needed to determine the optimal duration of secondary VTE prevention in patients with initial VTE provoked by minor transient or persistent risk factors (*see also* Figure 1). Studies are also needed to identify the highest risk minor transient or persistent risk factors.

Author's contributions

JM — sole author.

Conflict of interest

No conflict of interest declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments

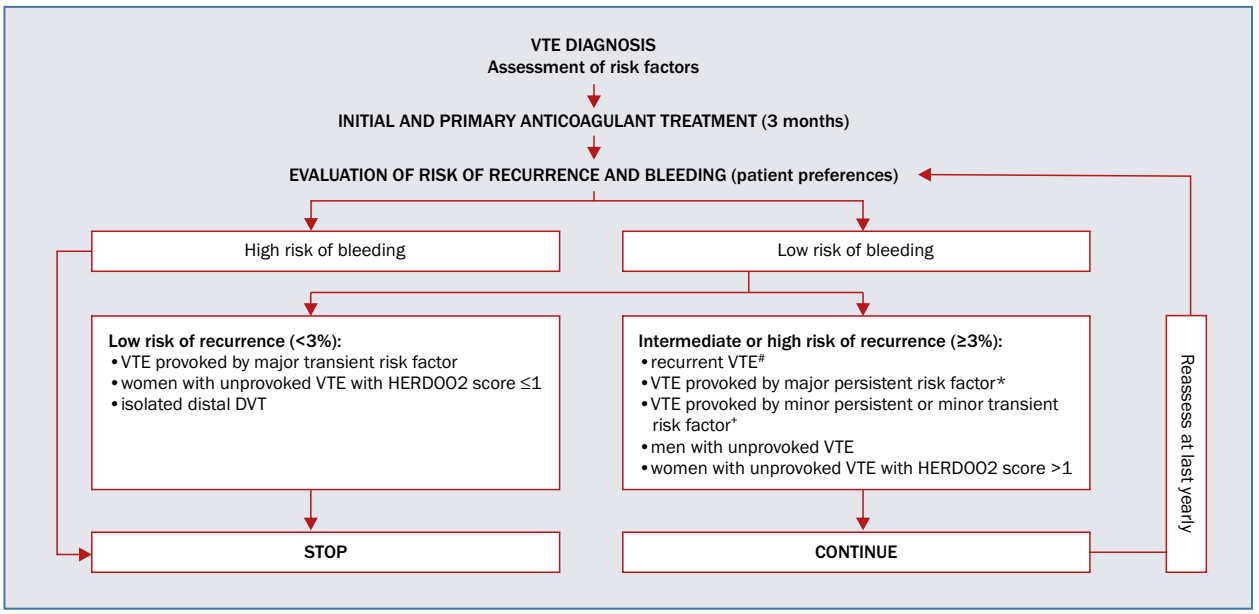

Figure 1. Approach to duration of anticoagulation in patients with venous thromboembolism (VTE) (modified after [7]); #previous VTE episode not related to a major transient or reversible risk factor; *see Table II; +see Table II and III; HERDOO2 — hyperpigmentation, edema, and redness in either leg; D-dimer ≥250 μg/L; body mass index ≥30 kg/m^2; age ≥65 years; DVT — deep vein thrombosis

involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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